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(54) Title: HERBAL FORMULATION AND THERAPEUTIC USES THEREFOR		
(57) Abstract The invention describes a herbal composition and its use for reducing/alleviating symptoms associated with arthritis, such as rheumatoid arthritis, osteoarthritis and reactive arthritis and for reducing the production of proinflammatory cytokines. Foods and beverages containing the herbal composition are also described.		

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HERBAL FORMULATION AND THERAPEUTIC USES THEREFOR

RELATED APPLICATION

This is a Continuation-in-Part application of U.S. Serial No. 08/691,865, filed August 2, 1996 (Notice of Allowance dated April 1, 1997), the teachings of which are incorporated by reference herein in their entirety.

BACKGROUND OF THE INVENTION

The manifestation of rheumatoid arthritis (RA) in humans is a consequence of a complex interplay of genetic and environmental factors. The disease is initiated following activation of T cells which is perpetuated when autoantigen reactive T cells and antigen presenting cells are generated. Consequently, autoantibodies (rheumatoid factors) which are directed against host's own immunoglobulins are produced. These processes are further complicated when proinflammatory mediators (such as IL-1, IL-6 and TNF- α) are produced in response to signals received from auto reactive T cells. As a result of these factors, the host loses the ability to control immune functions which results in final manifestation of the disease. The important role of TNF- α , IL-1 β and IFN- γ in exacerbating the disease process has been demonstrated in several animal models, and many investigators have aimed at regulating the production and synthesis of these proinflammatory mediators to control the disease. Thus, therapeutic approaches are targeted towards modifying the disease process.

Therapy for rheumatoid arthritis is focused around alleviating symptoms associated with the disease, such as

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relief of pain, reduction of inflammation and increasing range of motion. Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, naproxen, methotrexate) and glucocorticoids have been used to manage RA. However, these therapeutic agents have a variety of toxic side effects, such as gastric erosion and adverse effects on kidneys and liver, and may inadequately regulate the cellular immune functions and secretions of various cytokines. More recent therapeutic approach include the treatment of patients with multiple drugs has been proven to be more effective. There still remains a need for alternative therapies for the medical management of RA which can eliminate the need for traditional drugs and their associated side effects, particularly over prolonged daily use.

15 SUMMARY OF THE INVENTION

This invention describes an herbal composition and use of the herbal composition to reduce and alleviate symptoms associated with arthritis, such as rheumatoid arthritis, osteoarthritis and reactive arthritis. Also described is the use of the herbal composition to delay or significantly minimizing natural or induced aging of an individual. Another use for the novel composition is to reduce and/or ameliorate symptoms associated with Lyme disease. The herbal composition can be used to reduce the production of proinflammatory cytokines such as tumor necrosis factor (TNF), IL-1 and IL-6. Use of the herbal composition for the manufacture of a medicament for use in therapy or for the manufacture of a food or beverage is also described herein.

The formulation comprises an herbal extract from the roots, rhizomes and/or vegetation of six herbal plant varieties. In particular, the herbs are a combination of species of *Alpinia*, *Smilax*, *Tinospora*, *Tribulus*, *Withania*

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and *Zingiber*. A preferred formulation comprises *Alpinia galanga*, *Smilax glabra*, *Tinospora cordifolia*, *Tribulus terrestris*, *Withania somnifera* and *Zingiber officinale*, each present in a physiologically acceptable amount.

5 The herbal formulation can itself be administered, in a therapeutically effective amount, to an individual to alleviate symptoms associated with arthritis, or it can be used as an ingredient in foods and beverages which are designed for daily consumption as part of a therapeutic
10 regimen for arthritis, or as a prophylactic regimen for individuals having a genetic predisposition to arthritis. Suitable foods and beverages in which the herbal formulation can be incorporated within, without special processing requirements, include but are not limited to, nutritional
15 beverages, soft drinks, fruit beverages, baked goods, dips and spreads, salad dressings, puddings, condiments, confections, snack foods, ice cream, frozen confections and novelties, margarine-like spreads, seasonings such as for meat, poultry, seafood and salads, and non-baked, extruded
20 foods such as bars.

Daily ingestion of the formulation of this invention can replace or supplement traditional drug therapies and provides the patient suffering from arthritic symptoms with relief from joint stiffness, inflammation and improved joint
25 range of motion. The incorporation of the formulation into daily foods/beverages enables the patient to adhere to a daily therapeutic regimen in an unobtrusive manner and provides immediate therapeutic benefit.

DETAILED DESCRIPTION OF THE INVENTION

30 This invention is based upon the discovery of an herbal formulation that, when administered as part of a routine therapeutic regimen to individuals diagnosed with rheumatoid

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arthritis, has the ability to reduce/alleviate the physical symptoms associated with arthritis. The formulation of this invention comprises aqueous extracts from the roots, rhizomes and/or vegetation of the following herbs: *Alpinia* species, especially *Alpinia galanga* and *Alpinia officinarum*; *Smilax* species, especially *Smilax glabra*, *Smilax sarsaparilla* and *Smilax china*; *Tinospora* species, especially *Tinospora cordifolia*; *Tribulus* species, especially *Tribulus terrestris*; *Withania* species, especially *Withania somnifera*; and *Zingiber* species, especially *Zingiber officinale*.

The formulation of this invention is prepared by the aqueous extraction of roots, rhizomes and/or vegetation from the six varieties of herbs described herein. A detailed description of the extraction process and the preferred portion of the plant are provided in the Exemplification section. The term "extract" as used herein is intended to mean a concentrate of aqueous soluble plant components from the portion of the plant extracted and can be in aqueous or powdered form. After the extract from each herb is obtained (either liquid or powder form), they are admixed together in amounts that are physiologically acceptable to the patient. There are no special means for mixing required. The mixture of herbal extracts can be encapsulated, tableted or formulated with a physiologically acceptable vehicle into unit dosages.

A unit dosage can comprise a therapeutically effective amount of each herbal extract for a single daily administration (e.g., orally or by feeding tube in an enteral diet); or it can be formulated into smaller quantities of each ingredient to provide for multiple doses in a day. In either instance, the formulation of this invention can be manufactured into tablets, capsules, caplets, elixirs, enteral formulations or incorporated into slow-releasing

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carriers. Examples of physiologically acceptable vehicles include water, oil emulsions, alcohol or any of the food/beverage formulations described herein.

A unit dosage, as stated above, will depend upon many factors including age, condition and disease state of the patient and the number of times the unit will be taken in a single day. In any event, the entire daily dosage will be that which is physiologically acceptable to an individual and can be administered daily over a prolonged period of time. Physiologically acceptable amounts of each herb are as follows:

	<i>Alpinia galanga</i> :	from about 100 mg/kg/day to about 500 mg/kg/day;
15	<i>Smilax glabra</i> :	from about 50 to about 100 mg/kg/day;
	<i>Tinospora cordifolia</i> :	maximum of about 16 mg/kg/day;
	<i>Tribulus terrestres</i> :	from about 50 to about 100 mg/kg/day;
20	<i>Withania somnifera</i> :	maximum of about 100 mg/kg/day;
	<i>Zingiber officinale</i> :	maximum of about 2.5 mg/kg/day.

A preferred unit dosage of each herbal extract will be from about 2 to about 5 mg/kg/day. Thus, the total amount from all of the extracts will be from about 10 to about 30 mg/kg/day. This is well below the tolerance limit.

Alternatively, the formulation can be incorporated within or used on many of the foods and beverages one can consume on a daily basis. Suitable foods and beverages which could be made, include but are not limited to, nutritional beverages, soft drinks, fruit beverages and

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juices, electrolyte containing beverages, puddings, baked goods (i.e., cookies, brownies, fudge, cake, breads), non-baked extruded foods (i.e., bars), salad dressings, condiments, confections (i.e., candy), snack foods (i.e., chips, pretzels, tortillas), dips and spreads, ice cream, frozen confections and novelties, nutritional bars, margarine-like spreads, seasonings such as for meat, poultry, seafood and salads. Fat free, reduced fat and low calorie versions of these foods are embraced by this invention. Incorporation of the herbal composition into foods/beverages provides the advantages of patient compliance over a prolonged period of use and in a form which is more desirable to the consumer, rather than in the form of a medicament.

In a preferred embodiment, the herbal composition can be incorporated into a nutritional bar (e.g., non-baked, extruded), cookie or biscuit to provide a unit dosage of the composition of this invention. Other ingredients such as one or a combination of vitamins, minerals, proteins, dietary fats (as discussed below), carbohydrates, and other dietary supplements can be incorporated into the nutritional bar, cookie or biscuit depending upon the medical needs of the individual for whom the nutritional bar is intended. Flavors, coloring agents, spices, nuts and the like can be incorporated into the product.

The herbal compositions may be coformulated with dietary fats enriched with mono-unsaturated fatty acids, such as oleic acid, (e.g., sesame seed oil, olive oil, canola oil), linoleic acid (e.g., safflower oil) or with α -linolenic acid and γ -linolenic acid (e.g., black current seed oil, borage oil). Examples of suitable foods include margarine-like spreads, oil-in-water emulsions, salad dressings, and the like.

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A study was conducted on RA patients to determine the efficacy of the herbal formulation. The primary criteria in evaluating the efficacy was the degree of relief of pain and swelling and how the patients felt after taking the medication. After an eight week study of patients taking the herbal formulation orally, four times per day, patients reported improved range of motion in their joints and decreased swelling in one or multiple joints of the elbows, knees, ankles and hands. Chronic pain caused by the joint swelling had also been reduced.

Not only were physical changes observed in the patient group taking the formulation but there were positive chemical changes observed in the patients undergoing daily ingestion of this formulation. In general, a significant decrease in the elevated levels of proinflammatory cytokines (TNF- α , IL-1 β and IL-6) was considered indicative of a positive therapeutic effect. Proinflammatory cytokines (IL- β , TNF and IL-6) were measured in whole blood drawn from patients in the study at 0 and 8 weeks on the program. A significant decrease in these indicators was observed. These data coupled with physical improvement indicated that the herbal formulation was effective for alleviating symptoms of arthritis and can reduce the production of proinflammatory cytokines.

The herbal formulation contains ingredients derived from six herbs which influence various immune functions, such as curtailing inflammatory responses, improving cellular functions (e.g., decrease production of IL-1, TNF, IL-6 and reducing T and B cell functions) and curtailing the production of proinflammatory cytokines. With these immunological changes, a patient with arthritis is expected to physically improve in terms of pain and joint swelling within days on an oral or enteral therapeutic regimen.

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Reduction of pain and swelling and increased range of joint motion are expected over prolonged daily use of the formulation.

Other physical advantages are also possible with a daily ingestion of the formulation of this invention, such as resistance to common infections which typically trigger symptoms of arthritis. Erythrocyte sedimentation rate (ESR), an indicator of susceptibility to infection, was conducted on the rheumatoid arthritis patients who participated the study at 0 and 8 weeks. A significant decrease in ESR compared to basal levels was observed in patients taking the herbal formulation over the course of the study, thus indicating that the patients were less susceptible to infection, such as bacterial, viral or parasitic infections.

The benefit of down-regulating the production of pro-inflammatory mediators has importance for individuals other than those who have arthritis. For example, the formulation could be administered as a therapeutic or prophylactic for individuals who suffer from allergies and/or inflammation. For instance, it has been shown by the clinical study described herein that proinflammatory cytokines are down regulated and that B cells and T cells function can be down regulated. Other autoimmune diseases that are T-lymphocyte mediated can be similarly treated with the herbal formulation of this invention. Examples of other diseases include Crohn's disease, ulcerative colitis, systemic lupus erythematosus.

The novel formulations described herein can also be used to delay or significantly minimize the aging process of an individual. The term "aging process" is intended to embrace both the natural aging process as well as aging which is upregulated or exacerbated by systemic or chronic disease such as an autoimmune disease or chronic microbial

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(e.g., bacterial or viral) infection. In another use, the formulation can be administered to an individual suspected of, or diagnosed as having Lyme disease. The formulation can reduce and/or ameliorate the symptoms associated with
5 Lyme disease, particularly joint stiffness and inflammation.

Although the focus of the invention discussed above is for human therapy, it is also contemplated to use the herbal formulation of this invention as a therapeutic or prophylactic for non-human mammals, including domestic and farm
10 animals, having arthritis or other T cell mediated immune disease for which it is desirable to reduce/suppress immune response or alleviate joint pain and stiffness caused by these diseases. The skilled artisan would readily ascertain the mode and method of therapy based upon the animal to be
15 treated. For example, the herbal formulation can be incorporated into the animal's water source or feed, or it can be administered like a medicament in the form of a capsule, tablet, liquid or the like.

The invention will now be further illustrated by the
20 following non-limiting exemplification:

EXEMPLIFICATION

FORMULATION PREPARATION

The roots (*Smilax*, *Tribulus*, *Withania*), rhizomes (*Alpinia*, *Zingiber*) and/or whole plant (*Tinospora*) were
25 crushed into pieces, then soaked in water maintained at 60°C for overnight. The decoction was filtered, and concentrated using a custom made (industrial) roto-vapor using a 10 liter flask. The resultant paste was dried at 60°C in an oven for overnight to obtain dry powder. This procedure was followed
30 for all the extracts. The different dry powder extracts were mixed using a mixer, and the extracts were filled into gelatin capsules (0-size) using a capsule filling machine,

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as follows: 100 mg *Alpinia galanga*; 100 mg *Smilax glabra*; 100 mg *Tinospora cordifolia*; 100 mg *Tribulus terrestris*; 50 mg *Withania somnifera*; and 50 mg *Zingiber officinale*.

PATIENT STUDY

A panel of patients were interviewed and screened for physical symptoms of rheumatoid arthritis (RA). The patients were ranked on a scale of 1 to 8 for severity of their symptoms associated with RA. The criteria for the ranking included chronic pain and swelling in the joints of elbows, knees, ankles and hands. Patients experiencing pain and/or swelling in one joint were considered to have an score of 1, and the maximum score for patients who complained of pain and swelling in all the joints was 8. The results are summarized in the Table at the end of this section.

The patients were then tested for RA factor using the latex agglutination test described by Singer, J.M. and C.M. Plotz, *Am. J. Med.* 27:888-896 (1956) and Hansen et al., *Am. J. Clin. Pathol.* 73:110-113 (1980). Erythrocyte sedimentation rate (ESR) levels were also tested to determine whether a patient was resistant to infection. Only those patients who tested positive for RA factor were selected for the study.

All selected patients were required to refrain from taking any medication for three days immediately prior to the study, including NSAIDs. The patients were given a four-week supply of the herbal formulation and were asked to consume at least four capsules per day. The patients were asked to return for a clinical evaluation at 4 and 8 weeks after recruitment in the study. At week 4, patients were given a second four-week supply of the herbal formulation. Every patient was asked subjective questions about the pain

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and swelling in each joint, and the information was recorded. Any untoward side effects were also recorded. Based on the information obtained following subjective questioning, the RA score was calculated and the mean \pm standard error is shown in the Table. The RA factor testing and the ESR determinations were repeated on each patient at week 8.

CYTOKINES

The effects of consuming the formulation on the productions of various cytokines and interleukins was investigated to understand their effects on cellular functions based on the productions of various mediators. A significant decrease in the elevated levels of proinflammatory cytokines (TNF- α , IL-1 β , IL-6) and IL-10 was expected if the formulation exerted any significant therapeutic effect. An elevation in the levels of IL-10 which possess anti-inflammatory properties of down-regulating the levels of TNF- α , IL-1 β , IL-6 may be beneficial to RA patients. On the other hand, IL-10 could activate T cells leading to T-cell hypersensitivity. The production of IL-10 in response to both LPS (which accounts for IL-10 of non-T cell source; i.e., B cells and macrophages) was determined to understand functions of various cells and their response to the individual herbal components of the formulations.

On each patient visit, the venous blood samples were collected (between 9 and 11 am) from the patients and approximately 2 ml aliquots were transferred into 12 x 75 mm vacutainer tubes containing sodium EDTA. Lipopolysaccharide (LPS) from *E. coli* 055:B5 (Difco Labs, Detroit, MI) (1 ng/ml final concentration) was used as a stimulus for macrophages and B cells. Saline (0.9% w/v) (control) or LPS (0.05% v/v) were introduced in the tubes under sterile conditions using a tuberculin syringe. To prevent the blood

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from settling, the tubes were then placed on a varimix
 tilter (maintained at 30° angle, and tilting 100 times/hour)
 which was kept in a 37°C incubator. Plasma samples were
 separated at 0 hours (spontaneous), 8 hours or 24 hours
 5 after the initiation of incubation. The samples were stored
 at -20°C until the study was completed and then shipped on
 dry ice to a laboratory for analyses of cytokines using
 appropriate enzyme linked immunosorbent assay (ELISA) kits
 (Biosource International, Camarillo, CA) and used according
 10 to manufacturer's specifications (human TNF α : catalog no.
 KHC 3013; human IL-10: catalog no. KHC 0103; IL-6: catalog
 no. KHC 0063; IL-1 β : catalog no. 0012).

RESULTS

Consumption of the herbal formulation significantly
 15 decreased the proinflammatory mediators, ESR levels and
 provided relief of RA pains and swellings. The results are
 reported in the Table.

Table

Rx	TNF- α (pg/ml)	IL-1 β (pg/ml)	IL-6 (ng/ml)	IL-10 (pg/ml)	ESR (mm/h)	RA score
B-0	111 \pm 10	7.8 \pm 0.42	10.2 \pm 0.66	17.00 \pm 1.63	55.5 \pm 8.1	6.5 \pm 1.3
T-8	126 \pm 11	5.2 \pm 0.53*	7.8 \pm 0.75*	14.5 \pm 1.49*	26.5 \pm 3.5*	3.0 \pm 1.2

(*) indicates level of significance (P<0.05) compared to the basal levels as determined by matched paired t-test.

Data represents mean \pm standard error.

n = 33 patients

EQUIVALENTS

Those skilled in the art will recognize, or be able to
 ascertain, using no more than routine experimentation many
 equivalents to the specific embodiments of the invention
 5 described herein. Such equivalents are intended to be
 encompassed by the following claims:

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CLAIMS

We claim:

1. An herbal composition comprising an extract from roots,
rhizomes and/or vegetation of:
 - 5 a) *Alpinia*;
 - b) *Smilax*;
 - c) *Tinospora*;
 - d) *Tribulus*;
 - e) *Withania*; and
 - 10 f) *Zingiber*,each present in a physiologically acceptable amount.
2. An herbal composition comprising an extract from roots,
rhizomes and/or vegetation of:
 - 15 a) *Alpinia galanga*;
 - b) *Smilax glabra*;
 - c) *Tinospora cordifolia*;
 - d) *Tribulus terrestris*;
 - e) *Withania somnifera*; and
 - 20 f) *Zingiber officinale*,each present in a physiologically acceptable amount.
3. The composition according to Claim 1 or Claim 2 further
comprising a physiologically acceptable vehicle.
4. The composition according to any one of Claims 1 to 3
wherein the composition is in the form of a powder,
25 capsule, tablet, liquid, caplet or enteral formulation.
5. The composition according to any one of Claims 1 to 4
further comprising a dietary fat selected from the
group consisting of oleic acid, linoleic acid, α -

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linolenic acid, γ -linolenic acid and combinations thereof.

6. A food or beverage comprising the herbal composition according to any one of Claims 1 to 5.
- 5 7. Use of an herbal composition for the manufacture of a medicament for use in therapy, wherein the herbal composition comprises an extract from roots, rhizomes and/or vegetation of:
 - 10 a) *Alpinia*;
 - b) *Smilax*;
 - c) *Tinospora*;
 - d) *Tribulus*;
 - e) *Withania*; and
 - f) *Zingiber*,
 - 15 each present in a physiologically acceptable amount.
8. The use of Claim 7 wherein the therapy is for (i) reducing the production of proinflammatory cytokines; (ii) alleviating symptoms associated with arthritis; (iii) reducing erythrocyte sedimentation rate; (iv)
20 alleviating symptoms associated with Lyme disease; and (v) delaying and/or significantly minimizing natural or induced aging of an individual.
9. Use of an herbal composition for the manufacture of a food or beverage, wherein the herbal composition
25 comprises an extract from roots, rhizomes and/or vegetation of:
 - a) *Alpinia*;
 - b) *Smilax*;
 - c) *Tinospora*;
 - 30 d) *Tribulus*;

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- e) *Withania*; and
 - f) *Zingiber*,
- each present in a physiologically acceptable amount.
- 5 10. A method of making a food or beverage comprising incorporating into a traditional food or beverage formulation, an herbal composition comprising an extract from roots, rhizomes and/or vegetation of:
- a) *Alpinia*;
 - b) *Smilax*;
 - 10 c) *Tinospora*;
 - d) *Tribulus*;
 - e) *Withania*; and
 - f) *Zingiber*,
- each present in a physiologically acceptable amount.
- 15 11. A method for alleviating symptoms associated with arthritis comprising administering a therapeutically effective amount of the herbal composition according to any one of Claims 1 to 5 to an individual.
- 20 12. A method for reducing the production of proinflammatory cytokines in a mammal (e.g., human), comprising administering a therapeutically effective amount of the herbal composition according to any one of Claims 1 to 5.
- 25 13. A method for reducing the erythrocyte sedimentation rate in an individual, comprising administering a therapeutically effective amount of the herbal composition according to any one of Claims 1 to 5.
14. A method for alleviating symptoms associated with Lyme disease, comprising administering a therapeutically

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effective amount of the herbal composition according to any one of Claims 1 to 5.

- 5 15. A method for delaying and/or significantly minimizing natural or induced aging of an individual, comprising administering a therapeutically effective amount of the herbal composition according to any one of Claims 1 to 5.
- 10 16. The method according to any one of Claims 11 to 15 wherein the herbal composition is administered orally or by feeding tube in an enteral diet.

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/US 97/12872

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K35/78		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 15314 A (PHYTOPHARM LTD) 17 September 1992 see page 8, line 10 - line 24 ---	1-4,7,8
X	WO 91 08750 A (KRUEGER CHRISTIAN) 27 June 1991 see page 1, line 1 - page 4, line 14 ---	1-4,7,8
X	US 5 494 668 A (PATWARDHAN BHUSHAN) 27 February 1996 see column 10, line 10 - column 12, line 15 ---	1-4,7,8
X	US 5 529 778 A (ROHATGI SURENDRA) 25 June 1996 see column 1, line 14 - column 3, line 17 --- -/--	1-4,7,8
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
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Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">14 November 1997</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">03.12.97</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Rempp, G</div>

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 010, no. 098 (C-339), 15 April 1986 & JP 60 228419 A (KAO SEKKEN KK), 13 November 1985, see abstract ---	1-4,7,8
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INTERNATIONAL SEARCH REPORT

Int. l. application No.
PCT/US 97/12872

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-16
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No

PCT/US 97/12872

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